CASE REPORT

Atheroembolic renal disease as a cause of allograft primary non-function

Doença ateroembólica como causa de disfunção primária do enxerto renal

Helena Viana[1,2,3], Carina Ferreira[2,3], Fernanda Carvalho[1,3], Ana Rita Santos[1], Maria João Galvão[1], Francisco Remédio[2], Fernando Nolasco[2,3]

[1] Kidney Morphology Laboratory, Department of Nephrology, Hospital Curry Cabral, Lisbon, Portugal
[2] Kidney Transplant Unit, Department of Nephrology, Hospital Curry Cabral, Lisbon, Portugal
[3] CEDOC – Faculty of Medical Sciences, Universidade Nova de Lisboa, Lisbon Portugal

■ ABSTRACT

Atheroembolic renal disease, also referred to as cholesterol crystal embolization, is a rare cause of renal failure, secondary to occlusion of renal arteries, renal arterioles and glomerular capillaries with cholesterol crystals, originating from atheromatous plaques of the aorta and other major arteries. This disease can occur very rarely in kidney allografts in an early or a late clinical form.

Renal biopsy seems to be a reliable diagnostic test and cholesterol clefts are the pathognomonic finding. However, the renal biopsy has some limitations as the typical lesion is focal and can be easily missed in a biopsy fragment.

The clinical course of these patients varies from complete recovery of the renal function to permanent graft loss. Statins, acetylsalicyclic acid, and corticosteroids have been used to improve the prognosis.

We report a case of primary allograft dysfunction caused by an early and massive atheroembolic renal disease. Distinctive histology is presented in several consecutive biopsies. We evaluated all the cases of our Unit and briefly reviewed the literature.

Atheroembolic renal disease is a rare cause of allograft primary non-function but may become more prevalent as acceptance of aged donors and recipients for transplantation has become more frequent

Keywords: Allograft; atheroembolism; cholesterol; kidney.

■ RESUMO

A doença ateroembólica renal, é uma causa rara de falência renal, sendo secundária à oclusão das artérias renais, arteríolas e/ou glomérulos por cristais de colesterol com origem em placas de ateroma da aorta ou outras grandes artérias. Esta doença é, ainda mais raramente, causa de falência de enxerto renal, com manifestações precoces ou tardias.

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A biópsia renal permite um diagnóstico específico, através da identificação das "fendas de colesterol", patognomónicas desta patologia. No entanto, a biópsia apresenta limitações já que as lesões são focais e podem estar ausentes no fragmento renal.

A evolução clínica varia desde a completa recuperação até a permanente perda de função renal. As estatinas, o ácido acetilsalicílico e os corticóides têm sido utilizados de forma a melhorar o prognóstico.

Descrevemos um caso de disfunção primária de enxerto renal causada por extensa doença ateroembólica. As lesões específicas desta patologia são apresentadas, em sucessivas fases de evolução e em diversas biópsias. Reavaliámos os casos da nossa unidade de transplantação e revemos brevemente a literatura.

A doença ateroembólica é uma causa rara de disfunção primária do enxerto mas provavelmente tornar--se-á mais prevalente com o aumento da idade dos dadores/receptores aceites para transplantação.

Palavras-chaves: Ateroembolismo; Colesterol; Enxerto; Rim.

INTRODUCTION

Atheroembolic renal disease (AD) also referred to as cholesterol crystal embolization (CE) is a renal failure form that is secondary to occlusion of renal arteries, renal arterioles, and glomerular capillaries with cholesterol crystals[1]. It may rarely occur in renal allografts, in association with atherosclerosis. The source of emboli may be either the donor's or the recipient's vessels. This disease can occur as an early or a late cause of impaired renal allograft function and can be a rare cause of primary allograft dysfunction[2,3].

Renal biopsy is regarded as the definitive method for diagnosis[1]; however, the typical lesion (*i.e.*, arterial and capillaries blockage) usually is focal and can easily not be included in the biopsy fragment[4].

We report a case of primary kidney allograft dysfunction caused by AD. The distinctive histology is presented in several consecutive biopsies. We re-evaluated the renal cases of our Unit and briefly reviewed the literature.

CASE REPORT

A 51-year-old white female, with end-stage renal failure secondary to chronic pyelonephritis, underwent her first renal transplant. She had been on haemodialysis for 10 years, with panel reactive antibody of 12%.

The donor was a 56-year-old male, heavy smoker, with uncontrolled hypertension, deceased for cerebrovascular accident with haemorrhagic transformation. The surgical procedure was uneventful with cold and warm ischemia times of 17 h.20 min and 45 min., respectively. The surgeon described immediate diuresis, but noted a normal venous filling with some reduced organ perfusion. Zero-time biopsy was done with a semi-automatic 16G needle after arterial anastomosis. This biopsy revealed three glomeruli: one globally sclerosed and two normal. The fragment showed normal tubule-interstitial structure and an arciform artery with important intimal fibrous proliferation (Fig. 1A). Basiliximab (20 mg IV once) and metilprednisolone (500mg IV for 3 days) were used for induction immunosuppression. Maintenance immunosuppression consisted of tacrolimus (0.15 mg/kg/day), mycophenolate mophetil (1000 mg 12/12 hours) and prednisolone (20 mg/day).

At 24 hours, the patient presented allograft pain with diuresis reduction. The creatinine remained high (6.5 mg/dl) and the white cell count showed 11300/mm3 leucocytes without eosinophylia. Doppler ultrasound revealed renal artery and interlobular arteries systolic flow reduction and total lack of end-diastolic perfusion. The renal vein was permeable. At this time, low molecular weight heparin at anticoagulant therapeutic range was started, and tacrolimus was replaced by anti-thymocyte globulin, in order to maintain immunosuppression and reduce nephrotoxicity.

Seventh day biopsy revealed atheroembolic nephropathy (Fig. 2A) and acute tubular necrosis. The
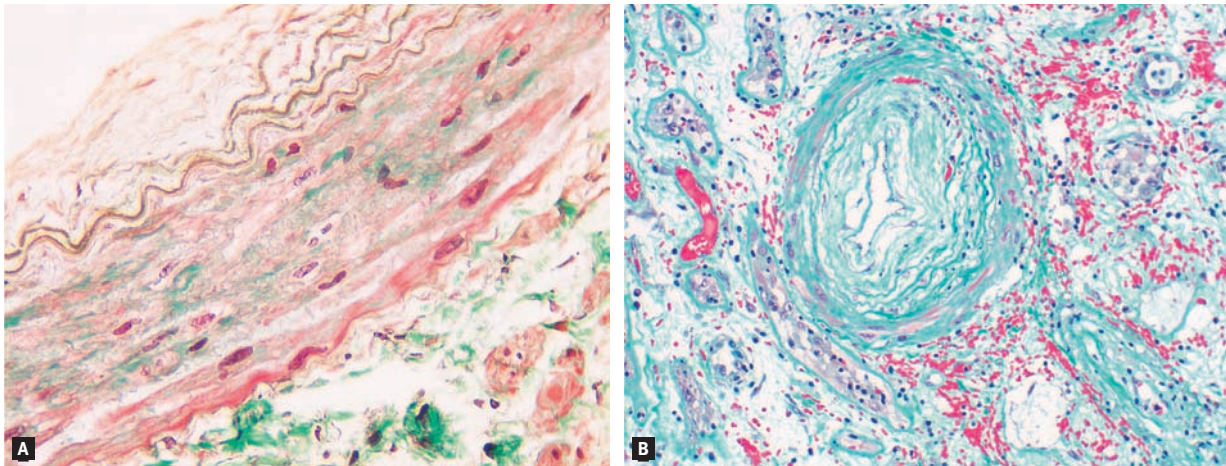
A – Zero-time biopsy (Masson Trichrome stain x400). **B** – Histology after nephrectomy (Masson Trichrome stain x100).
Large and medium artery presented intimal fibrosis and internal elastic duplication.

Figure 1

Atherosclerotic kidney disease.

fifteenth day Doppler ultrasound showed a global reduction of allograft vascularization, with slight improvement of systolic and diastolic flow in the renal artery and interlobular arteries. At the eighteenth day, donor specific anti-HLA antibodies were detected by Luminex® with a negative crossmatch by flow cytometry. At day 20, a new allograft biopsy showed acute rejection mediated by T-cells Banff IA superimposed in atheroembolic nephropathy (Fig. 2B). Methilprednisolone pulses (500mg/ IV in 3 consecutive days) were administrated, followed by seven days of intravenous immunoglobulin. The patient reached a diuresis of 1500 ml/day with 4.2 mg/dl of creatinine, requiring 2 haemodialysis sessions per week. The fourth biopsy, performed at the 37th day, demonstrated again cholesterol crystal embolization in medium arteries (Fig. 2C). At this time, the fragment showed ischemic glomeruli, tubular atrophy and interstitial fibrosis around the occluded vessels. Some areas presented acute tubular necrosis. Tacrolimus was replaced by sirolimus. The patient's clinical status did not change in the next two weeks and another biopsy at 54 post-transplant days was done before discharge. This biopsy showed cortical necrosis.

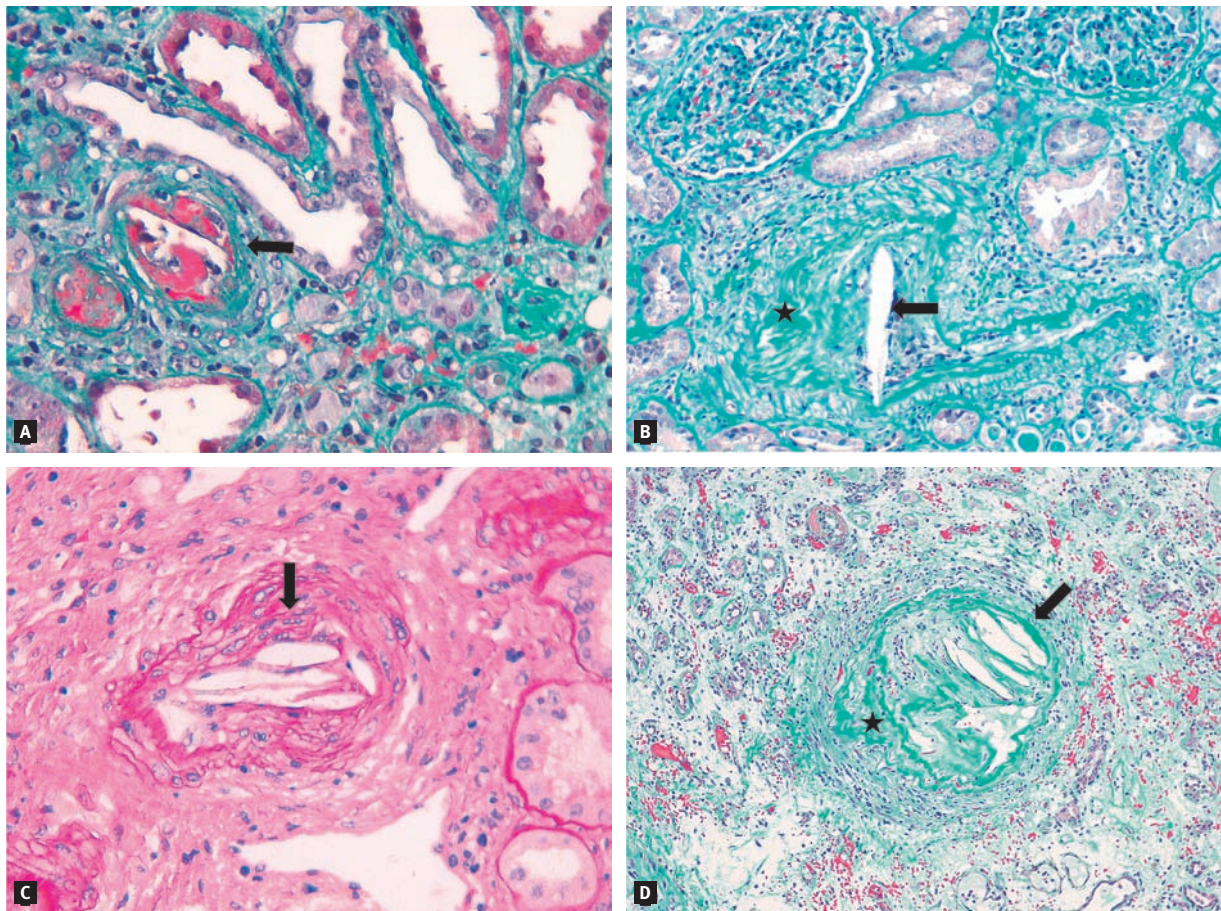The patient returned to ambulatory haemodialysis (two sessions/week), under sirolimus, mycophenolate of mophetil, prednisolone, statines and aspirin. In the following weeks, there was increased diuresis with effective azotemia reduction. Haemodialysis was stopped at day 120 after transplantation, with an estimated GFR of 20ml/min/1.73 m2.

Ten months after transplantation, the patient resumed haemodialysis. Nine months later, she was submitted to allograft nephrectomy for toxic rejection. Microscopy confirmed severe atherosclerosis and the presence of cholesterol crystal embolization in major arteries (Figs 2D and 1B).

■ DISCUSSION

■ Atheroembolic disease is rare in renal allografts.

Ripple *et al.* reported 7 cases among 1500 renal transplant biopsies (0.47%) performed at the Johns Hopkins Hospital, between 1984 and 1999[5], Modi *et al.*[4] review 200 renal transplant biopsies carried out, between 1990 and 1995, and found 2 cases of cholesterol embolism (1%). Lai *et al.*[6] reported that among 5435 renal allograft biopsies, 19 from 12

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A – 7th day biopsy (Masson Trichrome stain x400). B – 20th day biopsy (Masson Trichrome stain x200). C – 37th day biopsy (PAS x400). D – Histology after nephrectomy (Masson Trichrome stain x100).

All the biopsy demonstrated biconvex-shaped clefts (large arrow) occluding artery, witch characterize cholesterol emboli. Arterial myofibroblast proliferation (star) was presented in B and D.

Figure 2

Atheroembolic kidney disease observed in four consecutives biopsies.

cadaveric transplants (median age = 63 years) had AD (0.2%).

In our Unit we found four AD diagnosis (0.21%) among 1841 allograft biopsies. Three of the four biopsies belong to this case. The other biopsy is from a patient with a chronic allograft dysfunction.

Some authors[7-9] believe that cholesterol embolic disease is probably an under-reported cause of renal graft dysfunction. Meyrier[7] postulates that allograft

AD is more common in transplantation and often misinterpreted as acute/chronic rejection or calcineurin inhibitor toxicity.

■ **Cholesterol embolization: early vs. late form; donor vs. receptor origin.**

Renal cholesterol embolization can occur immediately before transplantation to 15 years post-transplantation[7]. However, two important clinical presentations[1] can be distinguished: early vs. late.

Primary dysfunction is commonly related to acute tubular necrosis; technical complications, such as arterial or venous renal thrombosis, ureteric obstruction or, rarely, hyperacute rejection. Nowadays, cholesterol embolization should also be considered in the differential diagnosis of early[3] allograft dysfunction. In these early cases, emboli are frequently released from the donor's arteries before or during organ harvesting. More rarely, early embolizations are originated from the recipient's atheromatous vessels during anastomosis. The early cases are essentially confined to the allograft, with less systemic manifestations.

The late clinical presentation can arise several years after transplantation, in stable grafts, where emboli often originate in the recipient's vessels. One of the largest known series of AD in renal allograft[6], a clinicopathological study of 12 cases, recognizes a recipient vs. donor origin ratio of 3:1. The late form of the disease is usually associated with the same mechanisms and risk factors as for the general population. Ulcerated aortic atherosclerotic plaques are stabilized by thrombus formation[10]. Therefore, any thrombus disruption increases the risk of embolization. The plaque trauma can result from direct instrumentation: angiographic catheters or surgical manipulation. Anticoagulants or thrombolytic agents that interfere with thrombus stability can also be responsible for cholesterol embolization[1,4]. Sometimes this late form can assume the same features of a systemic disorder, with multiple organ manifestations.

■ Histology

The pathognomonic finding in biopsy specimens[10] is the biconvex, needle-shaped cholesterol cleft. The crystals are normally dissolved during histological routine preparation, therefore, the cholesterol embolus[3] appears as characteristic clefts or "ghosts" (Fig. 2). The medium-sized arterioles (150 to 200 μm in diameter) and glomerular capillaries[3] are typically occluded. In the earliest phase, the histological lesions typically consist of the cholesterol clefts surrounded by eosinophilic material (Fig. 2A), without any endothelial cell reaction. Although some affected vessels may recanalize, cholesterol crystals can still be found within the vascular lumen. Over a period of time, the affected blood vessels are occluded

further from intimal hyperplasia and perivascular fibrosis[11]. Atheromatous occlusion of the medium-sized arteries and arterioles lead to ischemic injury and tissue infarction. Because of the ongoing ischemic injury, glomerular sclerosis, tubular atrophy, and interstitial fibrosis are frequent findings in the later stages of the disease[12]. Renal biopsy is a reliable diagnostic test in patients with cholesterol crystal embolization. However, the renal biopsy has some limitations. The typical lesion (*i.e.*, blockage of small arteries, arterioles and the glomerular capillaries), usually is focal and can easily not be included in biopsy fragments[4].

We think that the primary allograft dysfunction of our patient was caused by an early cholesterol embolization. The clinical data and the observation of zero-time biopsy suggested that the donor had severe and generalized atherosclerotic disease, so, probably the embolization originated in the donor. This atherosclerotic disease was later confirmed by nephrectomy. The surgical manipulation of the pre-existing donor atherosclerotic vessels was almost certainly the cause of the cholesterol embolization to the kidney allograft. Early after arterial anastomosis, the surgeon noted a reduction of allograft perfusion.

The diagnosis of typical histological lesions at the first week confirms without doubt the early form of AD. The clinical disease was confined to the allograft, without systemic manifestations, which is more usual in the early form. The acute tubular necrosis described at the seventh day biopsy and not present in the zero-time biopsy could be a histological feature of AD. The presence of cholesterol emboli in kidney vessels was documented in three consecutive biopsies and in the microscopy of nephrectomy. These observations indicated massive embolization with a widespread area of disease.

■ Prognosis and therapy

In native kidney, AD has been associated with poor renal and patient survival. Scolari *et al.*[13] followed 354 incident cases in native kidneys confirmed by histology or ophthalmoscopy until dialysis and death (mean follow-up time of 24 months). By the end of followup, 32.7% of patients were on dialysis; 1-year and 2-year patient survival were 83% and 75%, respectively.

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In allograft kidney, the clinical course of the disease also varies from complete recovery of renal function to permanent graft loss[3]. Several authors[7,11,12] conclude that AD with a recipient origin have better graft survival than AD with donor origin, that has a higher rate of graft dysfunction and subsequent graft loss. Graft failure is significantly associated with donor-derived and early AD[3,6]. The reason for this difference may be the more extensive AD developing in an atherosclerotic cadaveric donor during organ procurement or severe trauma leading to death[5].

Since the current tendency is to accept older donors and older recipients, with more advanced atherosclerotic disease, this condition is likely to become frequent in the future[3,11-13]. Particular care must also be taken during the evaluation of organ donors[13]. The vast majority of atheroemboli appear to originate from aortic atherosclerotic plaques, and it seems reasonable to avoid manipulation of the aorta as much as possible at implantation time[3,13].

The sources of therapeutic indications are from few longitudinal studies and some clinical data. There is no consistent data about therapy in allograft AD.

For the late manifestations, restricting indications for angiography and surgical procedures in atherosclerotic patients is important. Option for non-invasive diagnostic methods, such as MR angiography or computer-assisted tomographic angiography, could in part obviate the risk for catheter-induced embolization[1]. Scolari *et al.*[13] demonstrated that statin use was associated with better outcome when already in place at the time of AD diagnosis and when initiated after diagnosis. These drugs mediate plaque stabilization and regression through lipid-lowering and anti-inflammatory mechanisms, lowering risk for further embolization[14]. There is some rationale for the use of acetylsalicyclic acid, which attenuates platelet activation via cyclooxygenase-dependent pathways. Activation of complement (particularly C5) by cholesterol crystals *in vitro* and the clinical observation of low serum complement and peripheral eosinophilia strongly suggest a possible role for inflammation in the pathogenesis of AD[3]. If inflammation surrounding the cholesterol emboli is indeed the cause of progressive renal failure, there could be a potential role for the use

of steroids in this disease. Some authors recommended the usage of low-dose corticosteroids[15,16]. Other authors[17] noted improvement after the use of high-dose corticosteroids. However, use of steroids was not associated with outcome in the study of Scolari *et al.*[13].

There are numerous reports in the literature from experiments clearly showing an atherogenic effect of cyclosporine (CsA), by induction of endothelial dysfunction, endothelial cell injury, and arterial arteritis[18]. The literature regarding tacrolimus is sparse; nevertheless, a paper describes an important role for hydrogen peroxide in the tacrolimus nephrotoxicity[19].

Calcineurin-inhibiting (CNI) agents have been shown to induce oxidative stress while mycophenolate mofetil (MMF) has been shown to even ameliorate oxidative stress[20].

Consequently, application of CNI-free protocols in older patients receiving older organs appears to be the treatment of choice.

Autophagy is a protective mechanism involving degradation of oxidative intracellular material that occurs in atherosclerotic plaques. The regulation is dependent of mammalian target of rapamycin (mTOR), so that mTOR inhibitors activate autophagy and stabilize advanced atherosclerotic plaques[21]. These findings provide a rationale for the use of rapamycin or analogs in atheroembolic disease.

The use of protocol based in MMF and mTOR inhibitors without CNI seems more adequate in atherosclerotic patients receiving atherosclerotic organs.

Our patient presented extensive embolization of donor origin, in an allograft with chronic vascular lesions. The donor-derived and early AD dictated a poor prognosis and a diminutive probability of allograft recovery. The superimposed acute T-cell mediated rejection worsened the already poor basal allograft prognosis. The observations of cortical necrosis indicated lack of perfusions in some kidney areas. We used a statin, acetylsalicyclic acid and a more adequate immunosupressive protocol (high-dose corticosteroids, sirolimus and MMF without CNI) to improve allograft prognosis, without success.

CONCLUSIONS

In AD manifested as primary allograft dysfunction, emboli are frequently released from the donor's arteries before or during organ harvesting. More rarely, early embolizations are originated from the recipient's atheromatous vessels during the anastomosis. Atheroembolic disease is liquely to become more frequent in the future since donors and receptors are more olders and have more advanced atherosclerotic disease.

The vast majority of atheroemboli appear to originate from aortic atherosclerotic plaques, and it seems reasonable to avoid manipulation of the aorta as much as possible at implantation time.

Conflict of interest statement: None declared

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Correspondence to:

Helena Maria Morais de Sousa Viana
Department of Nephrology, Hospital Curry Cabral
Rua da Beneficência, nº 8, 1069-166
Lisboa, Portugal
E-mail: viana.helena@gmail.com